Remarks

It is submitted that the amendments to Claims 1-41 render moot the rejections under 35 USC §112, first and second paragraphs.

With respect to the rejection of Claims 1-41 under 35 USC §112, first paragraph, the Examiner refers to claims 32-35 and page 7 of the Specification relating to kits containing bowel cleanser, liquid diet powder, and optional flavor pack. The purpose of the optional clear liquid diet powders which may be used in conjunction with the administration of the compositions of the invention over a period of a day or more is to supply normal daily nutrients, not to ameliorate electrolyte imbalances caused by bowel cleansers. Such diets are commonly used in this art: note e.g., the Vining reference applied by the Examiner. They are also commonly used in arts other than bowel cleansing: e.g., oral surgery, where the patient is not allowed solid foods. A powder which can be reconstituted as clear bouillon is exemplary. This bouillon can also be prepared at home and taken with the same effect: satisfying hunger. It is not "fed back into the composition", it is food for the body.

Claims 32-35 have been amended to clarify that the liquid diet powder is a separate element in the kit, as is the optional flavor packet (see Examples). Flavor packs typically do not contain electrolytes (see, e.g., PDR *op.cit.* under GoLytely®). Neither of these compositions affects the basic characteristics of Applicant's invention: a palatable (or not unpalatable) effective, and safe bowel cleansing composition. Further, there are not enough electrolytes in a clear liquid diet powder dosage to counter any significant electrolyte imbalances caused by bowel cleansers, or to significantly adversely affect the properties of the composition, i.e., they would not materially change the novel characteristics of tastes tolerance and effectiveness of cleansing of Applicant's claimed compositions, described at length, *infra*.

The Examiner further states that the claims describe subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. The manner and process of making and using the inventions is extensively illustrated in the six Examples: 60g PEG powder and 18g of disodium phosphate powder are admixed and packeted. Two packets are orally administered in single dosages, one at 10 A.M. and one at 4 P.M.

In the Background of the Disclosure, pages 1 and 2, Applicant discusses known PEG bowel cleansers containing electrolytes - commonly referred to in the art as PEG-ELS cleansers - and the taste and side effects of these cleansers. As well known in the art, these are called isosmotic or isotonic electrolyte solutions containing sufficient serum electrolytes (NA^+, K^+) to counteract electrolyte imbalances (shifts, losses) caused by the large volumes of PEG which must be ingested. See e.g., PDR. *op.cit.* and of record, under Golitely® and Nulytely®.

On page 7 of Applicant's specification, it is stated that the PEG compositions of the invention can be used without supplemental electrolytes (the compositions of the inventions contain sodium ions from the NaP powders). Since the electrolytes of the known PEG-ELS solutions are the only electrolytes previously described, this disclosure clearly refers back to them, as would be apparent to anyone of skill in this art. These electrolytes are not present in the PEG powder/NaP powder compositions of the Examples.

Applicant's duty under this section of the code is to fully, clearly, exactly, and concisely describe the manner and process of making and using the invention. Applicant is not required to extensively describe art, in this case, PEG-ELS solutions, which has been known and commercially used for decades. Applicant has described properties of these prior art solutions attributable to their high electrolyte content, and has demonstrated that his compositions, without these electrolytes, are a significant improvement (see Examples - Results). This is sufficient.

It is submitted that claims 1 and 13 as amended, new claim 62, and the claims dependent thereupon, conform to the requirements of 35 USC §112, first paragraph, and reconsideration and withdrawal of this rejection is requested.

The Examiner further rejects claims 1-41 under 35 USC §112, second paragraph as indefinite. The Examiner is referred to Applicant's response to the §112, first paragraph, rejection, *supra*.

Accordingly, it is respectfully requested that these rejections under 35 USC §112 be reconsidered and withdrawn.

The Examiner has additionally rejected Claims 1-41 over WO 98/43654 (PCT) in view of Cleveland *et al.* (US 6,048,901); DiPalma *et al.* (Am J Gastroenterol 2002, 97:1776-1779); Wood *et al.* (US 5,498,425); Vining (US 5,782,762); Matsuoka *et al.* (Therapeutic Res 1996; 17:189-192); Sobrino-Faya *et al.* (Supplement to Gastroenterology 2002; 122:A-334); and Physicians' Desk Reference (PDR, 1995; 657-658 and 1018-1019, 49th Ed) as obvious under 35 §U.S.C. 103.

The claims were previously rejected on the same grounds over WO 98/43654 in view of Cleveland *et al.* '901, Wood *et al.* '425, Vining '762, Matsuoka *et al.*, Sobrino-Faya *et al.*, and PDR. Following Applicant's response to this rejection, all of the present claims were verbally allowed by the Examiner; this notification was then withdrawn and the same rejection applied to these claims with the addition of DiPalma *et al.* as a secondary reference. DiPalma *et al.* is merely cumulative and does not support the previous rejection as claimed by the Examiner and as discussed *infra*.

A. Applicant's claims are directed to bowel cleansing compositions and methods for cleansing the bowel with these compositions. The inventive compositions essentially contain polyethylene glycol (PEG) and sodium phosphate (Na/P), and substantially exclude added electrolytes conventionally found

necessary for preserving electrolyte balance in patients during bowel cleansing, as with PEG-ELS solutions.

Each of PEG and Na/P are themselves well-known in the art as bowel cleansers and laxatives. PEG is an osmotic pharmaceutical which, when used alone as a bowel cleanser, requires administration with large volumes of water to effectively purge the bowel (4 liters [approximately one gallon] of water in the course of one day for Golytely® and Nulytely®, (PDR, of record; or two liters for HalfLytely - www.drugs.com/HalfLytely.html - enclosed herewith). This amount of water if not counteracted, will disrupt the normal osmotic balance in the body, leading to overdilution of electrolytes in the blood plasma, particularly sodium (hyponatremia), and potential water intoxication (see, e.g., Wikipedia, "Water Intoxication", page 1 of 4, http://en.wikipedia.org/wiki/Water_in..., submitted herewith). Accordingly, for safety, PEG used alone is invariably prescribed for bowel cleansing as an osmotically balanced (isotonic) aqueous solution containing at least Na^+ and K^+ ions (PEG-ELS). These ions also counterbalance losses of electrolytes from body fluids as a result of the diarrhea induced by these purgatives (Wikipedia, op. cit. pg. 2). PEG-ELS, which entered the market in the 1980's, has since been the standard for bowel cleansing. However, it is also well-known that these products have an unpleasant salty taste due to the amount of electrolytes used. This unpleasant taste, combined with the volume and frequency of fluid the patient is required to ingest, and the commonly ensuing cramping, nausea, and bloating result in a high rate of patient non-compliance and ineffectively cleansed bowels, in turn leading to repeat colonoscopies or other measures (see Applicant's specification, page 2).

In contrast to PEG alone, aqueous Na/P alone (e.g., Fleet), is a hyperosmotic which provides high amounts of sodium in bowel cleansing formulations. The presence of these sodium ions can acutely elevate serum sodium concentrations (hypernatremia), a particular risk for patients with renal disease or other

complications. Na/P draws body fluid into the bowel by osmosis (electrolyte/fluid shift), and can increase serum sodium ion concentration enough to cause hypernatremia, the opposite of hyponatrenia (*supra*), but equally dangerous (PDR, of record, p. 1019, column 3: "Professional Use Warnings" and Wikipedia, op. cit; p. 2). This product also has an unpleasant taste and is associated with, *inter alia*, nausea and vomiting in use (Applicant's specification, p. 2); it also requires that a considerable amount of fluid to be taken with the composition to prevent dehydration. It is, however, a very good bowel cleanser.

Applicant claims a composition of PEG and Na/P, one hypoosmotic component (PEG) and one hyperosmotic component (Na/P). The hyperosmotic Na/P provides the compositions of the inventions with a saline osmotic effect which complements the effect of the hypoosmotic PEG component to provide a composition of a desirable osmolarity, without further addition of serum electrolytes as described on page 4, paragraph 3 of the specification. These compositions have many advantages, for example:

Large volumes of water, typically 4 liters per day for PEG-ELS, can be reduced to as little as 1 quart of water per dosage, twice per day for one day;

The unpleasant salty taste of PEG with electrolytes is eliminated or significantly reduced, and patient compliance is concomitantly increased;

Nausea, vomiting, bloating and other common patient complaints are virtually eliminated (see Examples);

Efficacy of the bowel prep is good to excellent (see Drawing); and

Frequency of dosages (e.g., two per day, preceding procedure with one quart water) is significantly reduced (compare, e.g., Golytely®, of record (PDR, p. 658): 8 oz. water every ten minutes until 4 liters of water are consumed).

B. The Examiner misconstrues the prior art. The art clearly distinguishes between laxative and purgative compositions,

while the Examiner combines them in the rejection as interchangeable. As well-known in the art, and as discussed on pages 1 and 2 of Applicant's specification, laxatives are formulated for long-term use to obtain regular bowel function, whereas bowel cleansers (purgatives) are formulated for rapidly emptying the bowel over a period of a few hours. While those unfamiliar with the physiology of the body might consider it predictable that the bowel can be safely and effectively cleansed by merely increasing the amount of any known laxative or combination of laxatives enough to accomplish this, this concept is clinically naive. As described above, any such enhanced compositions will indeed usually effectively cleanse the bowel, but they also may unpredictably have unpleasant and sometimes life-threatening effects on the human body.

The §103 rejection asserted by the Examiner relies on a combination of eight references, seven of which have been previously applied and overcome (*supra*). The Examine restates, "[T]he prior art amply suggests [Applicant's claimed inventions] as the prior art discloses the combination of PEG and sodium phosphate for use as a bowel cleanser and that PEG-3350 can be used without the electrolytes present in Golytely® and Nulytely® without there being changes in measured electrolytes." [Emphasis added.]

There is nothing whatsoever in the art relied upon that remotely suggests that the bowel cleansers Golytely® or Nulytely® can be safely used without electrolytes. The Examiner cites Cleveland *et al.* and DiPalma *et al.* to support his assertion that it is obvious that PEG 3350 can be used without balancing electrolytes in bowel cleansing compositions. Cleveland *et al.* (US 6,048,901) describe PEG compositions "without ancillary electrolytes" for use in treating symptoms of constipation; i.e., laxative compositions. (A detailed rebuttal of this previously applied reference is of record.) The newly applied reference authored by DiPalma *et al.* (wherein the "alia" include the Cleveland in the inventorship of the '901 patent), which is the grounds for reopening prosecution in this case, is cumulative.

The title of the DiPalma reference is "Overnight Efficacy of Polyethylene Glycol Laxative". DiPalma *et al.* clearly state the distinction between PEG bowel cleansing compositions and laxatives at page 1778, column 1: "PEG used as part of a balanced electrolyte solution for colon cleansing as PEG-ELS (polyethylene glycol-electrolyte solution) or PEG-SF-ELS (polyethylene glycol-sulfate-free-electrolyte solution) safely and effectively evacuates the colon. When cleansing solutions are used in smaller volume to treat constipation, the salts are absorbed, thereby negating the safe intent of lavage by an isotonic, poorly absorbed solution without net water or ion absorption or secretion... Safety and efficacy have been established for [our] PEG 3350 laxative for the short-term treatment of constipation." [Emphasis added.] Rather than suggesting that the electrolyte-free PEG-3350 used in the study can safely replace the PEG-ELS used in bowel cleansers such as Golytely®, DiPalma *et al.* confirm the conventional wisdom that electrolytes are necessary for a safe PEG bowel cleansing, and that such solutions cannot safely be used as laxatives: i.e., PEG and PEG-ELS are not interchangeable for laxative and bowel cleansing applications. The term "evacuation of the bowel" in DiPalma is loosely applied to both alleviation of constipation and to cleansing of the bowel; DiPalma's data and report apply, however, only to their PEG laxative, not to bowel cleansing.

Applicant's composition is a bowel cleansing composition comprising both PEG and Na/P, which does not require the balancing electrolytes for known in PEG solutions described in Applicant's specification, DiPalma *et al.*, and innumerable other publications throughout this art. It is the combination of Na/P with PEG, as required by Applicant's claims, and discussed at length supra, that permits Applicant's composition to be safely and effectively used as a purgative as described, without balancing electrolytes or additional bowel cleansing agents. There is nothing in the references relied upon by the Examiner that suggests this. The two most closely related references, Matsuoka *et al.* and Sobrino-Faya *et al.*, describe the use of a bowel cleansing composition

comprising PEG and Na/P. However, both include balancing electrolytes. Clearly, none of the authors of these publications considered that this combination would permit the elimination of the electrolytes heretofore presumed to be required for a safe bowel cleansing composition based on PEG.

As Applicant has discussed at length in the record, it is the absence of these electrolytes which eliminates or reduces (depending on taste) the unpalatability of conventional PEG bowel cleansers. Note, for example, DiPalma *et al.*: "Safety and efficacy have been established for PEG 3350 laxative for the short-term treatment of constipation... It is likewise accepted by patients because it is odorless, tasteless, and well-tolerated without gas or cramping." [Page 1778, column 1, emphasis added.] The Examiner is referred to Applicant's Examples, which report a clinical study conducted by Applicant wherein the composition administered contained 60gms PEG powder and 18 gm disodium phosphate, without electrolytes, to safely achieve bowel cleansing. All patients found the composition tolerable (Results). Compliance was universal and the cleansing was effective, as confirmed during bowel examination (Drawings). In contrast, DiPalma *et al.* describe clinical studies in constipated adult patients showing that a low daily dose of PEG alone is safe and effective for the treatment of constipation (page 1776, column 1).

With respect to the Woods *et al.* and Vining patents, Applicant claims liquid diets only in combination with the present inventions. Claims 10-12 were previously cancelled. With respect to the PDR publication, it appears to be irrelevant to the present issues. With respect to the PCT publication, WO 98/43654, Applicant has previously rebutted this reference at length in this prosecution. Applicant is not clear as to why the Examiner chose this as his primary reference in this Office Action, as, for example "to indicate that sodium phosphate can be combined with PEG to cleanse the colon", when Matsuoka *et al.* and Sobrino-Faya clearly state it. The gist of this rejection appears to be that the Examiner asserts that since polyethylene glycol and sodium

phosphate are mentioned and electrolytes are not, one of ordinary skill in the art would have been motivated to combine the phosphate with PEG to cleanse the colon without electrolytes. Since the Examiner cites no art whatsoever of the use of PEG for bowel cleansing without electrolytes, this is purely speculation on the Examiner's part. Cleveland *et al.* are discussed *supra* - this is a laxative composition which DiPalma *et al.* state cannot be used with electrolytes, although they are needed in PEG bowel-cleansing compositions. Thus one skilled in the art would assume that PEG in combination with at least any other osmotic cleanser in the PCT would require electrolytes. Of particular note is the disclosure of this PCT: it is directed to unrelated bowel cleansing compositions. The disclosure relates to combinations/permutations of magnesium, selected tartrates, and NaP for bowel cleansing. The added disclosure on which the Examine relies discloses nearly every known laxative/purgative in permutation and combinations in the hundreds. Claim 25 of this reference relates most closely to the present invention; it specifies "[a]n orally administrable non-aqueous composition capable of inducing purgation of the colon in comprising a purgative effective amount of a sodium phosphate salt... in combination with at least one composition [sic] selected from the group consisting of [*inter alia*, aqueous sodium phosphate salts, aqueous polyethylene glycol, and 27 additional specific candidates, including bran, aloe, and mineral oil]. This disclosure was clearly included as an attempt to preempt any uses of NaP with any other known laxative or purgative by the Assignee. Further, it is noted that a composition comprising aqueous PEG and NaP is not consistent with the definition of the claim 25 invention as an "orally-administrable non-aqueous composition", and that a dosage of the recited non-aqueous composition with NaP and PEG as per Applicant's dosage (or those of Matsuoka *et al.* or Sobrino-Faya, such as 10-30g NaP with 45 to 70 grams PEG could not be ingested without severe risk of choking. In sum, the PCT disclosure is garbled and non-enabling as to matter present in this

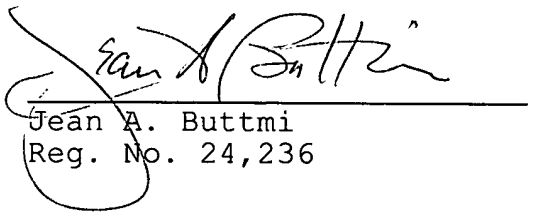
addendum, and no one even somewhat skilled in the art would refer to Claim 25 or the relevant part of the specification for guidance.

Applicant has invented and claims a novel, unobvious bowel cleansing composition and methods for bowel cleansing using this composition. It is safe; not unpalatable; requires only a low volume of fluid to for ingestion; and is a very effective bowel cleanser. There is nothing whatsoever in any of the references relied upon to suggest that the teachings thereof might be applicable to any of the other references. Further, it is well-understood in the patent law affecting biological sciences that predictability of medical outcomes is very low.

Applicant has noted supra, that the claims were previously verbally allowed by the Examiner over the combination of the WO 98/43654, Cleveland *et al.*, Matsuoka *et al.*, Sobrino-Faya *et al.*, PDR, Woods *et al.* and Vining prior art, under 37 CFR §103, and submits that the new ground of rejection relying on the teachings of DiPalma *et al.* to establish obviousness in view of the references of record fails to do so. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

The provisional rejection for double patenting is noted.

Respectfully submitted,



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